REMARKS

Claims 1-22, 25, and 27-33 are pending. Claims 1-6, 8-10, 12, 20, 21, 25, and 27-32 presently stand withdrawn as being drawn to non-elected subject matter. Applicants have cancelled claims13-18 and 33 without prejudice. Finally, Applicants have added new claims 34-39. Claims 1-12, 19-32, and 34-39 will therefore be pending upon entry of the proposed amendments.

I. Claim Amendments

Applicants have rewritten claims 7, 11, and 19 in independent form. In claim 7, Applicants have deleted the reference to claim 5 and incorporated steps a) through e) (inclusive) recited in claim 1. Similarly, in claim 11, Applicants have deleted the reference to claim 9 and incorporated steps a) through e) (inclusive) recited in claim 9.

New claims 34; 35; 36/39; 37; and 38 are based on claims 2; 3; 4; 5; and 6, respectively.

The foregoing amendments, which introduce no new matter, are being made for the sole purpose of expediting prosecution of the present application; and Applicants expressly reserve the right to pursue any of this cancelled subject matter in one or more continuing applications.

II. Response to "Election/Restrictions" portion of Office Action

According to the Office Action (Office Action, pages 2-3, italic and bold emphasis in original; underline emphasis added):

> Applicants have amended the claims such that they now read on reverse-immortalized human OEG cells. Thus, the Examiner agrees to the extent that the prior art of Ramon-Cueto does not anticipate or make obvious the instantly amended claims. However, the technical feature of the claims is considered to be reverse-immortalized human OEG cells, but this technical feature is not considered to be a *special* technical feature, because it does not make a contribution over the prior art of Barnett *et al.* (**Brain**, 123:1581-1588, 2000) when taken with Salmon *et al.* (**Mol. Therapy**, 2(4): 404-414, 2000, IDS) in further view of Halfpenny (**The Lancet Neurology**, 1: 31-40, 2002), which is found below. Thus, given that the technical feature of the claims do no contribute over the prior art, unity of invention is found to be lacking. Additionally, the Examiner notes that 37 CFR 13475(b)(3) [*sic.* 37 CFR 1.475(b)(3)] is directed to a specific combination of product, process of manufacture and use of said product. See also, MPEP § 1850, which states in part, 'When an application includes claims to more than one product, process, or apparatus, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the 'main invention' in the claims.' In the instant case, the first category is directed to a process of manufacture, not a product, as set forth in 37 CFR 1.475(b)(3).

This is respectfully traversed for at least any one of the independent reasons discussed below, and in doing so, Applicants expressly reserve their right to petition the finality of the present restriction requirement.

[A] The pending claims (i.e., those that are presently under examination and those presently assigned the "Withdrawn" status identifier) share a technical feature, which is **reverse-immortalised** human OEG cells that have the ability to promote axonal regeneration from adult CNS neurons. Contrary to the assertions of the Office, this technical feature is a special technical feature for at least the reasons provided in Applicants' traversal of the Office's 35 U.S.C. § 103 based on the Barnett, Salmon, and Halfpenny references mentioned above. It is therefore respectfully requested that the Office reconsider and withdraw the restriction

requirement in view of the aforementioned remarks (see pages 16-20 of this Amendment in Reply).

[B] Applicants also respectfully request that the Office reconsider and withdraw the restriction requirement for the following additional independent reason, which relates to the Office's apparent interpretation of certain passages within MPEP § 1850 and 37 CFR 1.475(b)(3). This is discussed in more detail below.

[1]

Claim 1 (presently withdrawn from consideration) is directed to a method of making a population of reverse-immortalised human olfactory ensheathing glia (OEG) cells, which have the ability to promote axonal regeneration from adult CNS neurons, for transplantation into a patient (for purposes of brevity only, the steps required by claim 1 are omitted here).

Claim 7 as presently amended is directed to a population of reverse-immortalised human OEG cells, which have the ability to promote axonal regeneration from adult CNS neurons, for transplantation into a patient, and which are producible by a method that includes the steps a) through e) as recited in claim 1.

[2] The Office, relying upon a passage from MPEP § 1850 (said passage restating, in part, the provisions of CFR 1.475(d)) appears to be asserting that the ordering of claim 1 (i.e., claiming a process of manufacture) and claim 7 (claiming a product) in Applicants' listing of claims precludes compliance with 37 CFR 1.475(b)(3). See Office Action at page 3 (emphasis added):

> Additionally, the Examiner notes that 37 CFR 13475(b)(3) [*sic.* 37 CFR 1.475(b)(3)] is directed to a specific combination of product, process of manufacture and use of said product. See also, MPEP § 1850, which states in part, 'When an application includes claims to more than one product, process, or apparatus, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the 'main invention' in the claims.' In the instant case, the first category is directed to a process of manufacture, not a product, as set forth in 37 CFR 1.475(b)(3).

Applicants respectfully disagree. The passage from MPEP § 1850 that is relied upon by the Office does **not** say that claims directed to a product, a process specially adapted for the manufacture of the said product, and a use of the said product need to be listed in exactly this (or any other order) order to satisfy 37 CFR 1.475(b)(3). Rather, the relevant rules speak to whether certain combinations of claims are present, but do not say that the aforementioned combinations of claims need to be arranged in any particular order. See, e.g., MPEP § 1850 (emphasis added):

> The method for determining unity of invention under PCT Rule 13 shall be construed as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application:
>
> (A) In addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product; or
>
> B) In addition to an independent claim for a given process, an independent claim for an apparatus or means specifically designed for carrying out the said process; or
>
> (C) In addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product and an independent claim for an apparatus or means specifically designed for carrying out the said process. ...
>
> As provided in 37 CFR 1.475(b), an international application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:
>
> (1) A product and a process specially adapted for the manufacture of said product; or
>
> (2) A product and process of use of said product; or
>
> (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
>
> (4) A process and an apparatus or means specifically designed for carrying out the said process; or
>
> (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

Moreover, the Office's apparent interpretation of certain passages within MPEP § 1850 and 37 CFR 1.475(b)(3) and assessment of unity of invention based thereon, appear to run afoul of PCT Rule 13.3, which states, in part (emphasis added), "Determination of Unity of Invention **Not Affected by Manner of Claiming**" as well as the MPEP's more general warning against the use of a "narrow, literal or academic approach" (MPEP § 1850) in determining unity of invention:

> Although lack of unity of invention should certainly be raised in clear cases, it should neither be raised nor maintained on the basis of a narrow, literal or academic approach.

As will be discussed in more detail below, the present claims, which share a special technical feature (*supra*), are directed to a product, a process specially adapted for the manufacture of the said product, and a use of the said product. As such, the present claims satisfy 37 CFR 1.475(b)(3) and therefore have unity of invention.

[3] The pending claims (i.e., those that are presently under examination and those presently assigned the "Withdrawn" status identifier) are unified and should therefore be examined in concert.

The present application is a U.S. National Stage application. As such, the present application is subject to unity of invention practice in accordance with 37 CFR 1.475 and 1.499 (see MPEP § 1896). In particular, see MPEP § 1850 (emphasis added):

> Therefore, when the Office considers international applications as an International Searching Authority, as an International Preliminary Examining Authority, and during the national stage as a Designated or Elected Office under 35 U.S.C. 371, PCT Rule 13.1 and 13.2 will be followed when considering unity of invention of claims of different categories without regard to the practice in national applications filed under 35 U.S.C. 111.

37 CFR § 1.475(b)(3) states that a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are

drawn to a combination of "[a] product, a process specially adapted for the manufacture of the said product, and a use of the said product" (*supra*). Here are claimed reverse-immortalised human OEG cells, which have the ability to promote axonal regeneration from adult CNS neurons (as well as cell lines and pharmaceutical compositions containing the same – claims 7, 11, 19, 21, 22, 25, and 27). Also claimed are processes specially adapted for the manufacture of said reverse-immortalised human OEG cells (claims 1 and 9 and claims dependent therefrom), as well as uses of said reverse-immortalised human OEG cells (claims 8, 12, 20, and 28-32). Applicants submit that the present claims, which share a special technical feature, satisfy 37 CFR 1.475(b)(3) and therefore have unity of invention. In view of the foregoing, Applicants respectfully request that the presently pending claims be examined in concert.

III. Independent Claims Presently Under Examination

Claim 7 as presently amended is directed to a population of **reverse-immortalised** human OEG cells, which have the ability to promote axonal regeneration from adult CNS neurons, for transplantation into a patient, and which are producible by a method that includes the steps a) through e) as recited in claim 1.

Claim 11 as presently amended is directed to a population of **reverse-immortalised** human OEG cells, which have the ability to promote axonal regeneration from adult CNS neurons, for transplantation into a patient, and which are producible by a method that includes the steps a) through e) as recited in claim 1.

Claim 19 as presently amended is directed to a **reverse-immortalised** human OEG cell, which has the ability to promote axonal regeneration from adult CNS neurons upon transplantation into a patient, produced by exposing a DNA construct within a reversibly-immortalised human OEG cell to a recombinase that excises the DNA construct by cleavage at the recombinase target sites.

Claim 22 is directed to a **reverse-immortalised** functional human olfactory ensheathing glia (OEG) cell line, which has the ability to promote axonal regeneration from adult CNS neurons.

IV. "Reverse-Immortalised" and "Reversibly-Immortalised" Cells

A "reverse-immortalised" cell is a cell that now exists in a non-immortalised state (see, e.g., claims 7, 11 and 19), which is directly obtained from a "reversibly-immortalised" cell (see definition below) by subjecting it to a further step of genetic modification.

A "reversibly-immortalised" cell is a cell that is presently in an immortalised state, but can be returned to a non-immortalised state at a later time (see, e.g., claims 13-17).

V. Rejections under 35 U.S.C. § 103

[A] Claims 7, 11, 13-17, and 19 are rejected for allegedly being unpatentable over "Barnett *et al.* (**Brain**, 123:1581-1588, 2000) when taken with Salmon *et al.* (**Mol. Therapy**, 2(4): 404-414, 2000, IDS) in further view of Halfpenny (**The Lancet Neurology**, 1: 31-40, 2002)" (Office Action, page 5). According to the Office Action (Page 6, bold emphasis added):

> Accordingly, in view of the combined art of Barnett and Salmon, it would have been obvious for the ordinary skilled artisan to modify the OEG cells, taught by Barnett, to produce **reversibly-immortalized** OEG cells, utilizing the methods of Salmon, with a reasonable expectation of success. One of ordinary skill in the art would be been sufficiently motivated to produce **reversibly-immortalized** OEG cells in order to produce a large number of therapeutic cells for transplantation, as suggested by Salmon (p. 404, Introduction) and further specifically suggested by Halfpenny who teach immortalized cell lines would provide sufficient numbers of cells for transplantation, which could yield large numbers of appropriate cells in homogeneity. See p. 34, col. 2, Immortalized Cell Lines.

The rejection of claims 13-17 are moot in view of the cancellation of claims 13-17. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 7, 11, and 19. Finally, it is respectfully requested that the rejection not be applied to new claims 34-39.

[1] Introduction

The claims presently under examination are directed to populations of **reverse-immortalised** human olfactory ensheathing glia (OEG) cells, which have the ability to promote axonal regeneration from adult CNS neurons, for transplantation into a patient, producible by the methods specified in the claims. The inventors have discovered that they can produce reverse-immortalised cells that have retained the ability of OEG cells to promote axonal regeneration (this again is a requirement of the present claims). In other words, **the fact that the cells have undergone immortalisation followed by desimmortalisation has not adversely affected this capacity of the cell**. The cells maintain their viability and functional properties after the excision of the transgene.

[2] Barnett et al.

Barnett et al discloses that human olfactory ensheating cells (OECs) have the ability to form new myelin sheaths following transplantation into areas of persistent demyelination in the adult rat CNS [page 1585, 2nd col., 2nd paragraph]. As acknowledged by the Office, however, Barnett et al makes no mention of reverse immortalized (a requirement of the claims) cells. Further, Barnett et al also fails to teach that their cells have the ability to promote axonal regeneration (also a requirement of the claims).

[3] Salmon et al.

As indicated in the Office Action, Salmon et al teaches methods for making **reversibly-immortalised cells** (see page 6 of the Office Action). Salmon describes an immortalisation process of some cells, but does not describe the desimmortalisation of reversibly-immortalised cells to obtain **functional** reverse-immortalised cells. In fact, Salmon's teachings would not have motivated an ordinary skilled artisan to try to obtain reverse-immortalised cells from reversibly-immortalised cells for the reasons set out herein.

Firstly, Salmon et al demonstrates transfection reversibility using excisable lentiviral vectors in HeLa cells (Excision of the Transgene and Conditional Ablation of Unexcised Cells, page 409). However, in this assay, the transgene transfected is not an oncogene, thus the transfected cells are **not** immortalized. Thus, the process as described in Salmon et al is not a desimmortalization process. Further, no reference is given whether the transfected cells using these vectors maintain their viability and functional properties after the excision of the transgene.

Additionally, Salmon et al describes the negative effect of the excision of oncogenes in the hLSEC (human liver sinusoidal endothelial cells) immortalised cells (which are a different cell type than the previously mentioned). Salmon et al explains that immortalised cells have a strict dependence on the presence of the immortalizing genes for cell division and that only unexcised cells proliferate (page 411, 1st col., 1st paragraph), so the cell cycle seems not to be maintained after the desimmmortalisation. Moreover, Salmon does not explain if the hLSEC cells maintain the functional characteristics described in the publication (page 409, 2nd col., 3rd par.) after the desimmortalisation step (i.e. after the excision of the oncogenes).

[4] Halfpenny et al.

Halfpenny et al. reviews the experimental myelin repair of different glial cells in diseases such as multiple sclerosis. However, Halfpenny et al does not consider the ability to promote axonal regeneration of these cells. In fact, according to Halfpenny et al:

> [T]he contribution of progressive axonal loss to secondary progressive multiple sclerosis mitigates against very late intervention since little can be expected of repair strategies when the axonal framework for remyelination has been lost [page 36, 2nd col., 3rd paragraph].

Therefore, in view of Halfpenny, a skilled artisan would not expect that immortalised glial cells as described in Halfpenny would be suitable to promote axonal regeneration after transplantation, as in view of the above, a skilled artisan would not have any expectation of repair or regeneration, when axonal loss already exists.

[5] Obviousness is a legal conclusion based on underlying findings of fact. When making a rejection under 35 U.S.C. § 103, the Office must provide some reason as to why the skilled artisan, at the time of filing, would have combined the elements of the claim in the manner required by the claims. *See Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350, 1356-1357 (Fed. Cir. 2007) (emphasis added):

> While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, **the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does**" in an obviousness determination. *KSR*, 127 S.Ct. at 1731.

The Office has argued:

> [I]t would have been obvious for the ordinary skilled artisan to modify the OEG cells, taught by Barnett, to produce reversibly-immortalized OEG cells, utilizing the methods of Salmon, with a reasonable expectation of success.

Applicants respectfully disagree.

As mentioned previously, the inventors have discovered that they can produce reverse-immortalised cells that have retained the ability of OEG cells to promote axonal regeneration, thereby providing populations of reverse-immortalised human olfactory ensheathing glia (OEG) cells, which have the ability to promote axonal regeneration from adult CNS neurons, for transplantation into a patient. As explained above, a "reverse-immortalised" cell is a cell that is directly obtained from a "reversibly-immortalised" cell by subjecting it to a further step of genetic modification. Thus, the cell now exists in a non-immortalised state.

Barnett et al discloses that human olfactory ensheating cells (OECs) have the ability to form new myelin sheaths following transplantation into areas of persistent demyelination in the adult rat CNS. Barnett et al makes no mention of reverse immortalized cells, nor does Barnett et al teach that their cells have the ability to promote axonal regeneration. From Salmon, one would have simply known that human liver sinusoidal endothelial cells can be reversibly immortalised using the lentivirus vector system. However, there is no teaching or suggestion in

Salmon that reverse immortalised hLSEC retain their functionality. The Office provides no reason as to why one would have combined the two very different disclosures of Barnett and Salmon, much less would have reasonably expected that doing so would have resulted in OEG cells that would have retained their functionality, i.e. their ability to promote axonal regeneration. In other words, one would not have reasonably expected from Barnett and/or Salmon that the neuroregenerative potential would be maintained after the desimmortalisation. That one would not have combined Barnett and Salmon is further reinforced by the teaching of Halfpenny et al because the skilled artisan would not have expected that immortalised glial cells as described in Halfpenny would be suitable to promote axonal regeneration after transplantation.

In summary, none of the prior of record art has shown successful reverse immortalisation of human CNS cells, let alone OEG cells. None of the prior art has shown or suggests that the ability of OEG cells to promote axonal regeneration is conserved during the immortalisation and after the desimmortalisation process. Salmon et al does not teach a desimmortalisation process to obtain the reverse-immortalised cells, which maintain their functional capacities. In view of the combined art of Barnett and Salmon, there would have been no reasonable expectation of success in promoting axonal regeneration using reverse-immortalised OEG of Barnett obtained through the method of immortalisation taught by Salmon. Moreover, Halfpenny would not have motivated the ordinary skilled artisan to use these glial cells to promote axonal regeneration after transplantation in humans.

In view of the foregoing, Applicants respectfully request that the rejection be reconsidered and withdrawn.

[B] Claims 18 and 22 are rejected for allegedly being unpatentable over "Barnett *et al.* (**Brain**, 123:1581-1588, 2000) when taken with Salmon *et al.* (**Mol. Therapy**, 2(4): 404-414, 2000, IDS) in further view of Halfpenny (**The Lancet Neurology**, 1: 31-40, 2002)" as applied to claims 7, 11, 13-17, 19 above and further in view of Franklin et al. (**Glia**, 17:217-224, 1996)" (Office Action, page 6).

The rejection of claim 18 is moot in view of the cancellation of claim 18.

Applicants respectfully request reconsideration and withdrawal of the rejection of claim 22 in view of the remarks below. The arguments presented above with respect to Barnett et al, Slamon et al, and Halfpenny et al also apply and are incorporated by reference herein. The foregoing remarks are supplemented here to address the inclusion of the Franklin et al reference.

Franklin et al. describes the use of a retrovirus containing the temperature sensitive (ts) mutant gene of the large T antigen (Tag). In this process, the authors do not excise the oncogene after the immortalisation because they argue that the immortalising gene product is not active following transplantation into the rat [page 218, 1st col., 3rd paragraph. Material and Methods]. Nevertheless, it is explained in the present application that the continued presence of the oncogene in these cells is of concern, in as much as it may increase the risk of malignant transformation following transplantation [paragraph 0013 of the published application].

One of ordinary skill in the art would not have been motivated to obtain a clonal reverse-immortalised human OEG cell line with expectation of success and with the enough safety to further transplantation in humans, utilizing the teachings of Franklin in combination with Barnett's, Salmon's and Halfpenny's teachings as explained above.

In view of the foregoing, Applicants respectfully request that the rejection be reconsidered and withdrawn.

The fee in the amount of $1,110 for Three Month Extension of Time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14829-0003US1/PC785647US.

Respectfully submitted,

Date: January 29, 2010

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